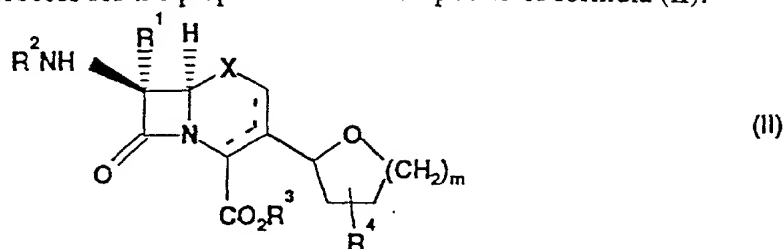
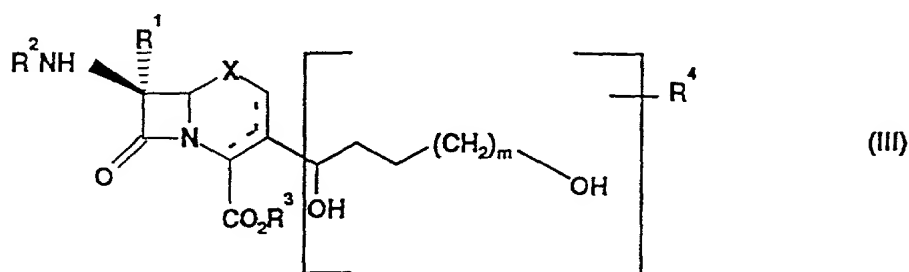


Claims:

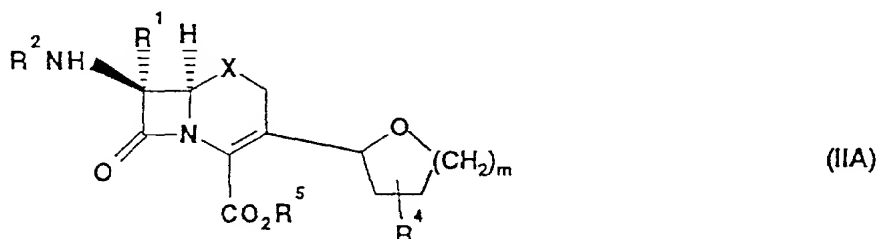
1. A process for the preparation of a compound of formula (II):



- 5 which includes the step of cyclising a compound of formula (III):

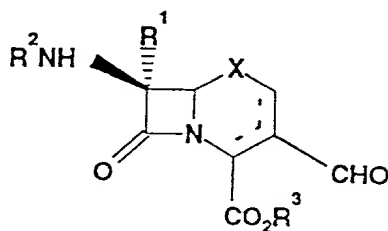


- wherein in formulae (II) and (III),  $R^1$  is hydrogen, methoxy or formamido;  
 $R^2$  is an acyl group;  $CO_2R^3$  is a carboxy group or a carboxylate anion, or  $R^3$  is a  
 10 readily removable carboxy protecting group;  $R^4$  represents hydrogen or up to four  
 substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino,  
 alkylamino, acylamino, dialkylamino,  $CO_2R$ ,  $CONR_2$ ,  $SO_2NR_2$  (where R is  
 hydrogen or  $C_{1-6}$  alkyl), aryl and heterocyclyl, which may be the same or different  
 and wherein any  $R^4$  alkyl substituent is optionally substituted by any other  $R^4$   
 15 substituent; X is S, SO,  $SO_2$ , O or  $CH_2$ ; and m is 1 or 2; and the dotted line indicates  
 that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and  
 where in formula (III) the substituent(s)  $R^4$  when other than hydrogen may replace  
 any of the hydrogen atoms bonded to carbon atoms in the side chain.
- 20 2. A process according to claim 1 wherein the compound of formula (II) is a 3-cephem of formula (IIA) or a pharmaceutically acceptable salt or pharmaceutically acceptable *in vivo* hydrolysable ester thereof:



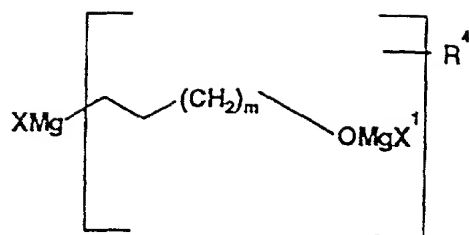
wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $m$  and  $X$  are as defined with respect to formula (II) and the group  $CO_2R^5$  is  $CO_2R^3$  where  $CO_2R^3$  is a carboxy group or a carboxylate anion.

3. A process according to claim 1 or 2 wherein  $X$  is S, O or  $CH_2$ .
4. A process according to any one of claims 1, 2 or 3 wherein the cyclic ether at the 3-position of the cephalosporin nucleus in formulae (II) and (IIA) is unsubstituted.
5. A process according to any one of claims 1 to 4 wherein  $m$  is 1, so that the cyclic ether at the 3-position in formulae (II) and (IIA) is a tetrahydrofuranyl system.
6. A process according to claim 5 wherein the cyclic ether at the 3-position in formulae (II) and (IIA) is an (S)-tetrahydrofuran-2-yl ring system.
7. A process according to any one of the preceding claims wherein in formula (III) when  $m$  is 1 the 1, 4-dihydroxylbut-1-yl side chain is the less polar diastereoisomeric form.
8. A process according to any one of the preceding claims wherein the cyclisation reaction of the process of the invention is carried out by treatment of the compounds (III) with an acid catalyst.
9. A process according to any one of claims 1 to 7 wherein the cyclisation reaction is carried out by treatment of the compounds (III) with an acylating agent.
10. A process according to any one of the preceding claims, wherein the compound of formula (III) is prepared by reacting a compound of formula (IV):



(IV)

with a compound of formula (V):



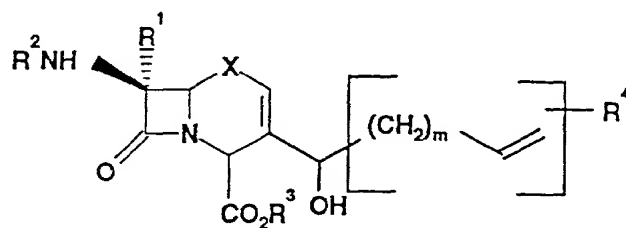
(V)

where  $R^4$  and  $m$  are as defined with respect to formula (III), and  $X$  and  $X^1$  are the same or different halogen, and the dotted line in formula (IV) indicates that the

5 compound (IV) may be a 2- or 3- cephem system.

11. A process according to any one of claims 1 to 10, wherein the compound of formula (III) is prepared by converting a compound of formula (IV) (as defined in claim 10) into a compound of formula (VIII):

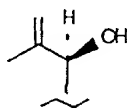
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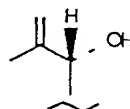
(VIII)

where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$   $m$  and  $X$  are as defined with respect to formula (III).

12. A process according to claim 11 wherein the compound of formula (VIII) has a hydroxyl group configuration (VIII A):



(VIII A)

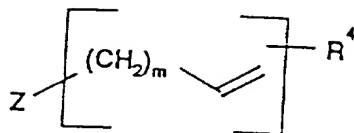


(VIII B)

20

13. A process according to claim 11 or 12 wherein the compound of formula (IV) is formed into a compound of formula (VIII) by reaction with an organometallic reagent.

14. A process according to claim 13 wherein the organometallic reagent is a compound of formula (IX):

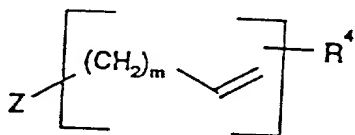


(IX)

where m and R<sup>4</sup> are as defined in formula (VIII), and Z is YMg where Y is a halogen.

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15. A process according to claim 11 or 12 wherein the compound of formula (VIII) is prepared stereospecifically from a compound of formula (IV) by the use of a compound (IX):

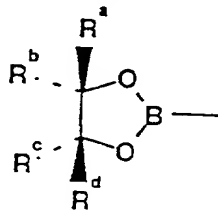


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(IX)

in which Z is a chirally inducing group which leads to preferential formation of a desired configuration of the hydroxyl group in the compound (VIII).

15 16. A process according to claim 15 wherein Z is the boronate group (X):



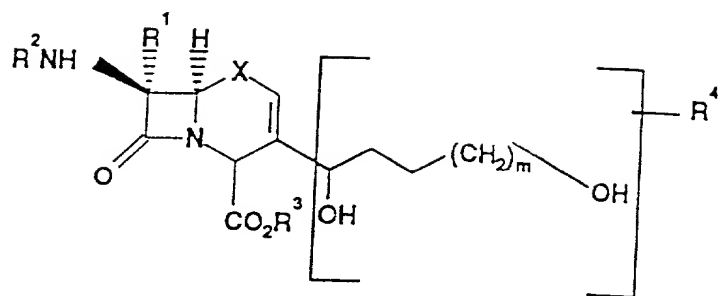
(X)

where R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup> and R<sup>d</sup> are independently selected from hydrogen, alkyl and protected carboxy.

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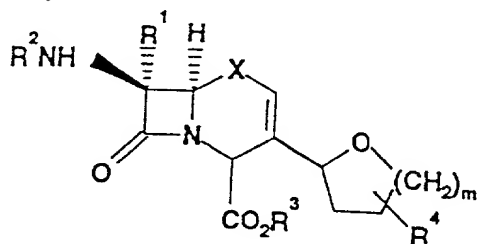
17. A process according to claim 16 wherein group (X) is a pinacol boronate group or a tartrate boronate group wherein R<sup>a</sup> is alkylcarboxylate, R<sup>b</sup> is hydrogen, R<sup>c</sup> is alkylcarboxylate and R<sup>d</sup> is hydrogen.

25 18. A process according to any one of claims 10 to 17 wherein the compound (IV) is converted into a 2-cephem compound of formula (III A):



(III A)

which is converted during the cyclisation process of the invention into a 2-cephem compound of formula (II B):



(II B)

where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $m$  are as defined in formulae (II) and (III) above, and the 2-cephem (II B) is then converted into a 3-cephem.

- 5
- 10
  19. A process according to any one of the preceding claims, substantially as hereinbefore described, with reference to the accompanying examples.
  20. The product of a process according to any one of claims 1 to 19.
- 15
  21. A compound of formula (II B), (III), (III A) or (VIII).